33. A method according to claim 30 wherein said target substance is a protease and said peptide inhibits said protease.

34. A method according to claim 33 wherein said protease is a caspase.

35. A method according to claim 33 wherein said protease is a interleukin 1 beta-converting enzyme.

36. A method according to claim 33 wherein said protease is a cysteine protease.

37. A method according to claim 33 wherein said protease is a serine protease.

38. A method according to claim 33 wherein said protease is a calpain.

39. A method according to claim 33 wherein said protease is a cathepsin.

40. A method according to claim 33 wherein said protease is a metalloproteinase.

41. A method according to claim 30 comprising administering a composition comprising said agent and a pharmaceutically acceptable carrier.--

REMARKS

Claims 12, 16, 17, 22 and 23-35 are pending. Claims 24-35 are newly added. An Appendix of Pending Claims is attached for the Examiner's convenience.

Support for amended claim 12 is found in the specification at page 11, lines 6-10. Claim 16 has been amended to correct a typographical error. Support for amended claim 16 is found in the specification at page 21, lines 8-9; page 22, lines 7-9. Claim 23 has been amended to remove the Markush group.

Support for newly added claims 24-29 is found in original claim 23. Support for newly added claim 30 is found in pending claim 12 and in the specification at page 20, line

27 through page 21, line 6, and at page 47, line4 through 48, line 17. Support for new claim 31 is found in pending claim 16. Support for new claim 32 is found in pending claim 17 and in the specification at page 20, line 27 through page 21, line 6, and at page 47, line4 through 48, line 17. Support for new claim 33 is found in pending claim 22. Support for new claim 34-40 is found in pending claim 23. Support for new 41 is found in the specification at page 47, lines 1-3.

As a preliminary matter, Applicants acknowledge that the obviousness-type double patenting rejection is being held in abeyance until allowable claims are found, at which point a terminal disclaimer will be filed.

Rejection Under 35 U.S.C. § 103(a):

The rejection of Claims 12, 16, 17, 22 and 23 under 35 U.S.C. § 103(a) as being unpatentable over Garlich et al. (U.S. Patent No. 5,133,965) in view of Watson (U.S. Patent No. 5,914,095) is maintained. Applicants submit that Garlich et al., combined with Watson, do not render amended Claims 12, 16, 17, 22 and 23 and newly added claims 24-29 unpatentable under 35 U.S.C. § 103(a).

Watson discloses bifunctional chelates that may comprise a protein. The protein component of Watson functions to concentrate the bifunctional chelates in a particular location (see Column 11, line 46 through Column 12, line 14). Thus, Watson *et al.* teach a method for concentrating an MRI agent in a particular location. However, Watson *et al.* do not disclose compositions comprising activatible MRI agents or methods for turning an MRI agent "off" by hindering the rapid exchange of water.

Garlich *et al.*, teach a method of delivering radionuclides linked to a high molecular weight metal binding protein for use in radiation ablation procedures. The protein component of Garlich *et al.*, is inert and is selected for its ability to bind metal cations (see Column 2, lines 25-64) and for its ability to remain at the site of injection (see Column 2, lines 9-21). There is no teaching in Garlich et al. of compositions comprising activatible MRI agents or methods for turning an MRI agent "off" by hindering the rapid exchange of water.

As amended, Claims 12, 16, 17, 22 and 23 recite activatible MRI agents. In other words, Claims 12, 16, 17, 22 and 23 disclose magnetic resonance imaging (MRI) contrast agents which detect the presence of a target substance as a result of an interaction between the target substance and the MRI agents of the invention. Prior to injection into a subject, the

MRI agents of the invention are relatively inactive, e.g. they are "off" and thus the region associated with the agent appears dark. However, upon interaction with a target agent, the MRI agents are activated, e.g. they turn "on" and enhance the observed image. See specification at page 20, line 27 through page 21, line 6.

Viewed simplistically, this "trigger" mechanism, whereby the contrast agent is "turned on" by the delivery of the blocking moiety is based on a dynamic equilibrium that affects the rate of exchange of water molecules in one or more coordination sites of the paramagnetic metal ion contained in the MRI contrast agents of the present invention. In turn, the rate of exchange of the water molecule is determined by the presence or absence of at least one blocking moiety on the MRI agent. Thus, in the presence of the blocking moiety, the complexes of the invention that chelate the paramagnetic ion have reduced coordination sites available that can rapidly exchange with water molecules of the local environment. In such a situation, the water coordination sites are substantially occupied or blocked by the coordination atoms of the chelator and at least one blocking moiety. Thus, the paramagnetic ion has essentially no water molecules in its inner-coordination sphere. Because all the coordination sites of the metal ion are blocked or occupied with moieties other than water molecules, there is little if any net enhancement of the imaging signal by the metal ion complexes of the invention.

However, when at least one of the inner-sphere coordination sites on the metal ion complex becomes available as a result of the removal of the blocking moiety, the water molecules of the local environment are able to reversibly occupy the inner-sphere coordination site or sites, causing an increase in the rate of exchange of water and relaxivity of the metal ion complex toward water thereby producing a bright or enhanced image. Thus, claims 12, 16, 17, 22 and 23-29 teach compositions and methods comprising activatible MRI agents, i.e., MRI agents that can be turned "on" and "off" as a means of enhancing the image produced by an MRI contrast agent.

When rejecting claims under 35 U.S.C. § 103, the Examiner bears the burden of establishing a *prima facie* case of obviousness. *See, e.g., In re Bell*, 26 USPQ2d 1529 (Fed. Cir. 1993); M.P.E.P. § 2142. To establish a *prima facie* case, three basic criteria must be met. First, the prior art reference, or references when combined, must teach or suggest each and every limitation of the rejected claims. *See, e.g.,* M.P.E.P. § 706.02(j). Second, the

skilled artisan, in light of the teachings of the prior art, must have a reasonable expectation that the modification or combination suggested by the Examiner would be successful. *See, e.g., In re Dow*, 5 USPQ2d 1529, 1531-32 (Fed. Cir. 1988). Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify or combine the teachings of the reference in the manner suggested by the Examiner. *See, e.g., In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). The teaching or suggestion to make the claimed invention, as well as the reasonable expectation of success, must come from the prior art, not Applicant's disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); M.P.E.P. § 706.02(j). If any one of these criteria is not met, *prima facie* obviousness is not established.

The Examiner states that the references were combined because both disclose DOTA analogs capable of being conjugated to a site directed macromolecule such as a peptide and attached to a metal for magnetic resonance imaging. Applicants submit that there is no suggestion or motivation either in the references themselves or in the knowledge available to one of skill in the art to modify or combine the teachings of Garlich *et al.*, and Watson as neither reference teaches activatible MRI agents.

Based on the teachings of Watson and Garlich *et al.*, a skilled artisan would have no reasonable expectation of success of making an MRI agent of the present invention. In particular, the present invention teaches magnetic resonance imaging (MRI) contrast agents that are relatively inactive, e.g. they are "off" until they interact with a target substance. As a result of the interaction between the target and the blocking moiety, the MRI agents are activated, e.g. they turn "on" and enhance the observed image. See specification at page 11, lines 6-10; and at page 20, line 27 through page 21, line 6.

In addition, as can be seen from the above discussion, neither Garlich *et al.*, or Watson teach each and every element of the present invention. Specifically, neither reference, alone or in combination teaches activatible MRI agents. Applicants respectfully request that the rejection of claims 12, 16, 17, 22 and 23 under § 103(a) be withdrawn.

Attached hereto is a marked-up version of the changes made to the specification and claims by this Amendment. The attached page is captioned **"Version with markings to show changes made."**

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Dated: 6/5/02

Respectfully submitted,

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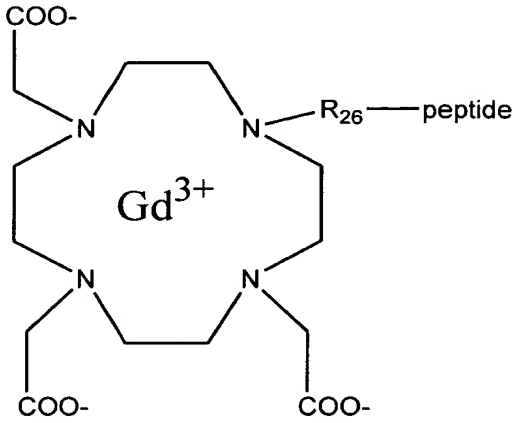
"VERSION WITH MARKINGS TO SHOW CHANGES MADE"

Claim 12 has been amended as follows:

12. (Twice Amended) An activatible MRI agent having the formula:



wherein R_{26} is a linker.

Claim 16 has been amended as follows:

16. (Thrice Amended) An MRI agent according to claim 12 wherein R_{26} comprises -((CH$_2$)CO)-.

Claim 22 has been amended as follows:

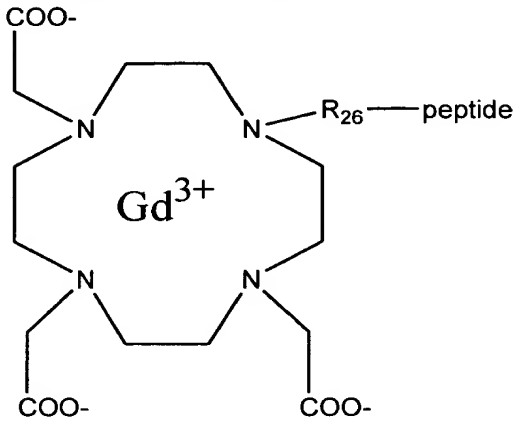
22. (Amended) An MRI agent according to claim 12 wherein said target substance is a protease and said peptide inhibits [a]said protease.

Claim 23 has been amended as follows:

23. (Amended) An MRI agent according to claim 22 wherein said protease is [selected from the group consisting of] a caspase[, interleukin 1 beta-converting enzyme, cysteine protease, serine protease, calpain, cathepsin and metalloproteinase].

Appendix of Pending Claims

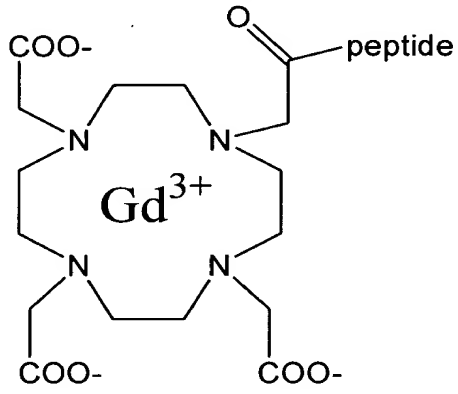
12. (Twice Amended) An activatible MRI agent having the formula:



wherein R_{26} is a linker.

16. (Thrice Amended) An MRI agent according to claim 12 wherein R_{26} comprises -[$(CH_2)CO$)-.

17. An MRI agent according to claim 16 having the formula:



22. (Amended) An MRI agent according to claim 12 wherein said target substance is a protease and said peptide inhibits [a]said protease.

23. (Amended) An MRI agent according to claim 22 wherein said protease is [selected from the group consisting of] a caspase[, interleukin 1 beta-converting enzyme, cysteine protease, serine protease, calpain, cathepsin and metalloproteinase].

--24. An MRI agent according to claim 22 wherein said protease is a interleukin 1 beta-converting enzyme.

25. An MRI agent according to claim 22 wherein said protease is a cysteine protease.

26. An MRI agent according to claim 22 wherein said protease is a serine protease.

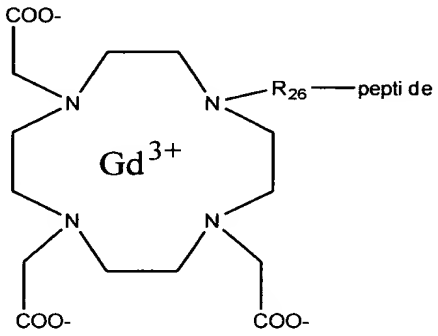
27. An MRI agent according to claim 22 wherein said protease is a calpain.

28. An MRI agent according to claim 22 wherein said protease is a cathepsin.

29. An MRI agent according to claim 22 wherein said protease is a metalloproteinase.

30. A method of simultaneously delivering an activatible MRI agent and acquiring an MRI image comprising:

a) administering an activatible MRI agent to a tissue, cell or patient, said MRI agent having the formula:



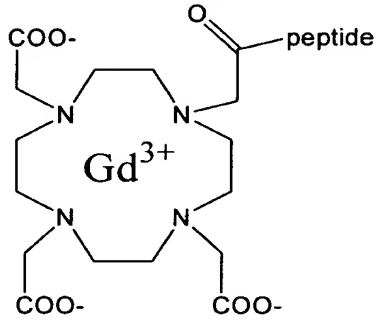
wherein R_{26} is a linker; and,

under conditions whereby said peptide interacts with a target substance in said tissue, cell or patient such that the rapid exchange of water in at least one coordination site of said agent is increased, and,

b) acquiring a magnetic resonance image of said cell, tissue or patient.

31. A method according to claim 30wherein R_{26} comprises -((CH$_2$)CO)-.

32. A method of according to claim 30, said MRI agent having the formula:



33. A method according to claim 30 wherein said target substance is a protease and said peptide inhibits said protease.

34. A method according to claim 33 wherein said protease is a caspase.

35. A method according to claim 33 wherein said protease is a interleukin 1 beta-converting enzyme.

36. A method according to claim 33 wherein said protease is a cysteine protease.

37. A method according to claim 33 wherein said protease is a serine protease.

38. A method according to claim 33 wherein said protease is a calpain.

39. A method according to claim 33 wherein said protease is a cathepsin.

40. A method according to claim 33 wherein said protease is a metalloproteinase.

41. A method according to claim 30 comprising administering a composition comprising said agent and a pharmaceutically acceptable carrier.